Serial No.: 09/500,162
Applicant: Poirier, J.

NON-AD

Filing Date: 02/08/00
Priority Date: 12/16/96-CON
10/16/96-CIP
04/26/95-PCT

AD ONLY

AD ONLY

Search Strategy

```
     FILE 'USPATFULL'

                E POIRIER JUED/IN
L1            5 S E2
L2          638 S (APO E OR APOE)
L3          171 S L2 AND NEUROLOG?
L4          164 S L3 AND DISEASE
L5           19 S L4 AND (APOE/CLM OR APO E/CLM)
L6           16 S L5 NOT L1

     FILE 'WPIDS'

L7          131 S (APO E OR APOE)
L8            7 S L7 AND (NEUROLOG?)
                E POIRIER J/IN
L9           41 S E3
L10           4 S L9 AND APOLIPOPROTEIN

     FILE 'MEDLINE'

                E ROSES A D/AU
L11         320 S E3
L12         118 S L11 AND (APO? OR APOLIPROTEIN)
L13          14 S L12 AND NEUROLOG?
L14          75 S L12 AND (APOE)
L15           5 S L14 AND REVIEW?
L16           5 S L15 NOT L13
                E SCHMECHEL D E/AU
L17          71 S E3
L18          50 S L17 NOT L11
L19           4 S L18 AND (APOLIPOPROTEIN OF APOE)
                E AMOUYEL P/AU
L20         159 S E3 OR E5
L21          54 S L20 AND (APO OR APOLIPOPROTEIN)
L22           1 S L21 AND NEUROLO?
L23           4 S L21 AND PY=1996
L24           5 S L21 AND PY=1995
L25           4 S L21 AND PY=1994
L26           2 S L21 AND PY=1993
L27           1 S L21 AND PY=1992
L28           5 S L21 AND PY=1997
L29           6 S L21 AND PY=1998
L30           5 S L21 AND PY=1999
                E SEVIGNY P/AU
L31           8 S E3
                E NICOLL J A R/AU
L32          96 S E1 OR E2
L33          39 S L32 AND (APO OR APOLIPOPROTEIN)
L34       25198 S APOLIPOPROTEIN OR APO
L35         129 S L34 AND PARKINSON?
L36          15 S L35 AND (THRAP? OR TREAT?)
L37         114 S L35 NOT L36
```

L1 ANSWER 5 OF 5 USPATFULL
1999:92499 Apolipoprotein E polymorphism and treatment of Alzheimer's disease.
Poirier, Judes, Boisbriand, Canada
McGill University, Montreal, Canada (non-U.S. corporation)
US 5935781 19990810
WO 9529257 19951102
APPLICATION: US 1997-727637 19970221 (8)
WO 1995-CA240 19950426 19970221 PCT 371 date 19970221 PCT 102(e) date
PRIORITY: GB 1994-8465 19940427
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a method for the identification of human subjects to be responsive to cholinomimetic therapy comprising determining the absence of apolipoprotein E4 (apoE4) alleles in a biological sample of the patient where the absence of at least one apoE4 allele indicates a predisposition to respond to cholinomimetic therapy and methods of administering cholinomimetics to such identified subjects.

CLM What is claimed is:
1. A method for the identification of human subjects with cognitive impairments to be responsive to a cholinomimetic drug comprising determining the number of copies of apoE4 gene alleles in said subject and wherein the absence of at least one apoE4 gene allele indicates a predisposition to respond to a cholinomimetic drug.

2. A method of treating human subjects with cognitive impairments comprising identifying a subject according to the method of claim 1 and administering a therapeutically effective amount of a cholinomimetic drug wherein administration of the cholinomimetic drug improves cognitive performance.

3. The method of claim 2 wherein said cholinomimetic drug is selected from the group consisting of inhibitors of acetylcholine degradation, inducers of acetylcholine synthesis, acetylcholine agonists or mimics, and muscarinic M2-receptor antagonists.

4. The method of claim 1 wherein the number of copies of apoE4 gene alleles is determined indirectly by determining the presence of apoE2 and/or apoE3 gene alleles using appropriate apoE2 and apoE3 probes.

L1 ANSWER 4 OF 5 USPATFULL
2000:15459 Methods for assessing the prognosis of a patient with a neurodegenerative disease.
Poirier, Judes, Boisbriand, Canada
Nova Molecular Inc., Montreal, Canada (non-U.S. corporation)
US 6022683 20000208
APPLICATION: US 1996-766975 19961216 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method for the determining the appropriate therapy and/or prognosis for a patient diagnosed with a non-Alzheimer's disease (AD) neurological disease based upon the patient's apoE allele load. The invention also provides a method for the identification of human subjects with a non-AD neurological disease that are likely to respond in clinical trials that test pharmaceuticals useful in the treatment of neurological diseases.

CLM What is claimed is:

1. A method for determining the prognosis and ability of a patient diagnosed with a non-Alzheimer's disease (non-AD) neurological disease to respond to therapy comprising the following: a) identifying a patient who has been diagnosed with a non-AD neurological disorder; b) determining the apolipoprotein E (apoE) allele load of said patient through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and c) utilizing the data obtained from step b) in a prognostic protocol; wherein the presence of at least one apoE .epsilon.4 allele in said patient is indicative of said patient having a poor prognosis of recovery and a decreased responsiveness to therapy.

2. The method of claim 1, wherein said method further comprises obtaining a patient profile.

3. The method of claim 1, wherein said patient is diagnosed with a disease selected from the group consisting of prion diseases, a pathology of the developing nervous system, a pathology of the aging nervous system, nervous system injury, coma, infection of the nervous system, a dietary deficiency, and a cardiovascular injury.

4. The method of claim 3, wherein said prion disease is Creutzfeldt-Jakob disease.

5. The method of claim 3, wherein said patient has been diagnosed with a congenital defect in amino acid metabolism.

6. The method of claim 5, wherein said defect is selected from the group consisting of arginosuccinic aciduria, cystathionuria, histidinaemia, homocystinuria, hyperammonaemia, phenylketonuria, and tyrosinanaemia.

7. The method of claim 3, wherein said patient has been diagnosed with fragile X syndrome.

8. The method of claim 3, wherein said patient has been diagnosed with a disease selected from the group consisting of neurofibromatosis, Huntington's disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, stroke, Parkinson's disease, and multiple infarcts dementia.

9. The method of claim 2, wherein said patient profile includes a determination of said patient's sex.

10. The method of claim 2, wherein said patient profile includes the patient's genotype.

11. The method of claim 10, wherein said patient's genotype is the presenilin genotype.

12. The method of claim 10, wherein said patient's genotype is the apolipoprotein C1 (apoC1) genotype.

13. A method of characterizing the genotype of a patient diagnosed with a non-Alzheimer's disease (non-AD) neurological disease who is in a clinical trial for the treatment of a non-AD neurological disease comprising the following: a) determining the apolipoprotein E (apoE) allele load of a patient who has been diagnosed with a non-AD neurological disorder through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and b) utilizing the data obtained from step a) in a prognostic protocol.

14. A method for determining the ability of a patient with a non-Alzheimer's disease (non-AD) neurological disease to respond to cholinomimetic therapy comprising the following: a) determining the patient profile of said patient; b) determining the apolipoprotein E (apoE) allele load of said patient through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and c) utilizing the data obtained from step b) to assess the patient's responsiveness to cholinomimetic therapy; wherein a patient lacking both apoE .epsilon.4 alleles is expected to benefit from cholinomimetic therapies.

L1 ANSWER 3 OF 5 USPATFULL
2001:105165 APOLIPOPROTEIN E POLYMORPHISM AND TREATMENT OF ALZHEIMER'S DISEASE.
POIRIER, JUDES, BOISBRIAND, Canada
US 2001006784 A1 20010705
APPLICATION: US 1999-342993 A1 19990629 (9)
PRIORITY: GB 1994-8465 19940427
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed herein are methods for identifying a patient for the treatment of cognitive impairments.

CLM What is claimed is:
1. A method for the identification of human subjects to be responsive to a cholinomimetic drug, said subjects having Alzheimer's disease, said method comprising determining the number of copies of apoE4 gene alleles in said subject, wherein the absence of apoE4 gene allele in a biological sample of said subject indicates a predisposition to respond to a cholinomimetic drug.

2. The method of claim 1, wherein said method further comprises administering to said subject having an absence of apoE4 allele a therapeutically effective amount of a cholinomimetic drug.

3. The method of claim 2, wherein administration of the cholinomimetic drug improves cognitive performance.

4. A method for identifying a patient sample in a clinical trial of a drug for the treatment of cognitive impairments, said method comprising: (a) identifying a patient already diagnosed with said cognitive impairments, or as being predisposed to acquire or to be at risk for said cognitive impairments; and (b) determining the number of copies of apoE4 gene alleles in said patient, wherein an absence of apoE4 allele places the patient into a subgroup for said clinical trial of said drug.

5. A method for identifying a patient sample in a clinical trial of a drug for the treatment of Alzheimer's disease, said method comprising: (a) identifying a patient already diagnosed with said disease or as being predisposed to acquire or to be at risk for said disease; and (b) determining the number of copies of apoE4 gene alleles in said patient, wherein an absence of apoE4 allele places the patient into a subgroup for said clinical trial for the treatment of said Alzheimer's disease.

6. A method for identifying a patient sample in a clinical trial of a cholinomimetic drug for the treatment of a disease, said method comprising: (a) identifying a patient already diagnosed with said disease, or as being predisposed to acquire or to be at risk for said disease; and (b) determining the number of copies of apoE4 gene alleles in said patient, wherein an absence of apoE4 allele places the patient into a subgroup for said clinical trial for the treatment of said a

disease.

L1 ANSWER 2 OF 5 USPATFULL
2001:131318 Methods for increasing ApoE levels for the treatment of neurodegenerative disease.
Poirier, Judes, Boisbriand, Canada
McGill University, Montreal, Canada (non-U.S. corporation)
US 6274603 B1 20010814
APPLICATION: US 1998-160462 19980924 (9)
PRIORITY: US 1997-59908P 19970924 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed herein is a method for reducing neurodegenerative disease in patients by administration of a therapeutically-effective amount of a compound which can increase ApoE levels.

CLM What is claimed is:
1. A method of treating a neuronal deficit in a patient, said patient diagnosed with Alzheimer's disease or having a predisposition to Alzheimer's disease, said method comprising administering a therapeutically-effective amount of a composition comprising probucol or an analog of probucol, said composition being a composition which increases ApoE levels.

2. The method of claim 1, wherein said method further comprises administering a second compound, said second compound comprising probucol analogs, vitamin E, donepezil, blood pressure inhibitors, antioxidants, anti-inflammatories, or steroids other Than estrogen.

3. The method of claim 1, wherein said therapeutically effective amount of a composition is sufficient to increase ApoE levels by about 10% or more.

4. The method of claim 1, wherein said therapeutically effective amount of a composition is sufficient to increase amyloid scavenging by ApoE.

5. The method of claim 1, wherein said patient is presymptomatic.

6. The method of claim 1, wherein said patient has at least one apoE4 allele.

7. The method of claim 1, wherein said administering further includes administering tacrine to said patient.

8. The method of claim 1, wherein said administering further includes administering estrogen to said patient.

9. The method of claim 1, wherein said administering further includes administering donepezil to said patient.

10. A method of increasing ApoE polypeptide levels in a patient diagnosed with Alzheimer's disease or having a pedisposition to Alzheimer's disease, said method comprising administering a therapeutically-effective amount of a composition comprising probucol or an analog of probucol.

11. The method of claim 10, wherein said patient has at least one apoE4 allele.

12. The method of claim 10, wherein said composition further comprises a

compound comprising probucol analogs, tacrine, heptylphysostigmine, simvastatin, lovastatin, pravastatin, thorvastatin, vitamin E, donepezil, blood pressure inhibitors, antioxidants, anti-inflammatories, or steroids.

13. The method of claim 10 wherein said composition further includes one or more compounds comprising, vitamin E, donepezil, blood pressure inhibitors, antioxidants, anti-inflammatories, or steroids.

14. The method of claim 10, wherein said ApoE polypeptide levels are measured by quantitating ApoF polypeptide levels.

15. The method of claim 10, wherein said ApoE polypeptide levels are measured by quantitating ApoE polypeptide levels with an antibody.

16. The method of claim 10, wherein said increasing is in brain tissue or human cerebrospinal fluid of said patient.

L6 ANSWER 16 OF 16 USPATFULL
96:31717 Methods of screening for Alzheimer's disease.
Roses, Allen D., Durham, NC, United States
Strittmatter, Warren J., Durham, NC, United States
Salvesen, Guy S., Chapel Hill, NC, United States
Enghild, Jan, Durham, NC, United States
Schmechel, Donald E., Durham, NC, United States
Duke University, Durham, NC, United States (U.S. corporation)
US 5508167 19960416
APPLICATION: US 1994-227044 19940413 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of diagnosing or prognosing Alzheimer's disease in a subject are disclosed. The methods involve directly or indirectly detecting the presence or absence of an apolipoprotein E type 4 (ApoE4) isoform or DNA, encoding ApoE4 in the subject. The presence of ApoE4 indicates the subject is afflicted with Alzheimer's disease or at risk of developing Alzheimer's disease. A novel immunochemical assay for detecting the presence or absence of the Apoliprotein E (ApoE) E4 allele in a subject is also disclosed.

CLM What is claimed is:
1. A method of detecting if a subject is at increased risk of developing late onset Alzheimer's disease (AD) comprising directly or indirectly: detecting the presence or absence of an apolipoprotein E type 4 isoform (ApoE4) in the subject; and observing whether or not the subject is at increased risk of developing late onset AD by observing if the presence of ApoE4 is or is not detected, wherein the presence of ApoE4 indicates said subject is at increased risk of developing late onset AD.

2. A method according to claim 1, wherein said detecting step is carried out by collecting a biological sample containing DNA from said subject, and then determining the presence or absence of DNA encoding ApoE4 in said biological sample.

3. A method according to claim 2, wherein said determining step is carried out by amplifying DNA encoding ApoE4.

4. A method according to claim 3, wherein said amplifying step is carried out by polymerase chain reaction.

5. A method according to claim 3, wherein said amplifying step is carried out by ligase chain reaction.

6. A method according to claim 1, wherein said detecting step is carried out by collecting an ApoE sample from said subject, and then detecting the presence or absence of the ApoE4 isoform in said ApoE sample.

7. A method according to claim 1, wherein said detecting step is carried out by isoelectric focusing.

8. A method according to claim 1, wherein said detecting step is carried out by immunoassay.

9. A method according to claim 1, wherein said detecting step is carried out by immunoassay with an antibody that selectively binds the ApoE4 isoform.

10. A method according to claim 1, wherein said subject has previously been determined to have one or more factors indicating that such subject is afflicted with Alzheimer's disease.

11. A method according to claim 1, wherein said detecting step comprises detecting whether said subject is homozygous for the gene encoding ApoE4.

12. A method useful as an aid in determining the prognosis for late onset Alzheimer's Disease (AD) of a subject, said method comprising: detecting the presence or absence of an apolipoprotein E type 4 isoform (ApoE4) in the subject; observing that (i) the subject's prognosis is more negative for late onset AD if the presence of ApoE4 is detected than if it is absent, or that (ii) the subject's prognosis is more positive for late onset AD if ApoE4 is absent than if it is detected.

13. A method according to claim 12, wherein said detecting step is carried out by collecting a biological sample containing DNA from said subject, and then detecting the presence or absence of DNA encoding ApoE4 in said biological sample.

14. A method according to claim 12, wherein said detecting step is carried out by polymerase chain reaction or ligase chain reaction.

15. A method according to claim 12, wherein said detecting step is carried out by collecting an ApoE sample from said subject, and then determining the presence or absence of the ApoE4 isoform in said ApoE sample.

16. A method according to claim 12, wherein said detecting step is carried out by isoelectric focusing.

17. The method of claim 12, wherein the subject's prognosis is most negative if the subject has more than one allele for ApoE4.

18. A method of detecting if a subject is at increased risk of developing late onset Alzheimer's disease comprising directly or indirectly: identifying the apolipoprotein E type isoforms in the subject; and observing if the presence of an apolipoprotein E type 4 isoform (ApoE4) is or is not detected, such risk being increased in subjects where ApoE4 is detected over subjects in which ApoE4 is absent.

19. A method according to claim 18, wherein said identifying step is carried out by determining the apolipoprotein E type isoforms present in a biological sample containing DNA from said subject.

20. A method according to claim 19, wherein said determining step is carried out by amplifying DNA encoding ApoE4.

21. A method according to claims 20, wherein said amplifying step is carried out by polymerase chain reaction.

22. A method according to claim 20, wherein said amplifying step is carried out by ligase chain reaction.

23. A method according to claim 18, wherein said identifying step is carried out by collecting an ApoE sample from said subject, and then detecting the presence or absence of the ApoE4 isoform in said ApoE sample.

24. A method according to claim 18, wherein said identifying step is carried out by isoelectric focusing.

25. A method according to claim 18, wherein said identifying step is carried out by immunoassay.

26. A method according to claim 18, wherein said identifying step is carried out by immunoassay with an antibody that selectively binds the ApoE4 isoform.

27. A method according to claim 18, wherein said subject has previously been determined to have one or more factors indicating that such subject is afflicted with Alzheimer's disease.

L6 ANSWER 15 OF 16 USPATFULL
1998:48182 Method of prognosing chronic neurodegenerative pathology following a head injury.
Roberts, Gareth Wyn, Harlow, England
Graham, David Ian, Glasgow, Great Britain
Nicoll, James Alan Ramsey, Glasgow, Great Britain
SmithKline Beecham p.l.c., Brentford, England (non-U.S. corporation)
US 5747260 19980505
WO 9603656 19960208
APPLICATION: US 1997-776356 19970225 (8)
WO 1995-EP2828 19950713 19970225 PCT 371 date 19970225 PCT 102(e) date
PRIORITY: GB 1994-15073 19940727
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of prognosing a head-injured subject or a subject who may be at risk of sustaining a head injury for the likelihood that a head injury might give rise to a chronic neurodegenerative pathology which could result in neuropsychological, psychiatric or neurological deficits, the method comprising detecting the presence or absence of ApoE isoforms or of DNA encoding ApoE isoforms in the subject.

CLM What is claimed is:
1. A method of prognosing in a head-injured subject or a subject who may be at risk of sustaining a head injury for the likelihood that a head injury might give rise to a chronic neurodegenerative pathology which could result in neuropsychological, psychiatric or neurological

deficits, the method comprising detecting, using an in vitro or ex vivo assay, the presence or absence of the ApoE isoform ApoE4 or of DNA encoding for the ApoE isoform ApoE4 in the subject, the presence of at least one ApoE4 allele being prognostic of increased risk for neuropsychological, psychiatric or neurological deficits in a head injured patient or one at risk of sustaining a head injury and the absence of an ApoE4 allele being prognostic of minimal increased risk for neuropsychological, psychiatric or neurological deficits.

2. A method according to claim 1 wherein said detection step involves collecting a sample of biological material containing DNA from the subject.

3. A method according to claim 2, wherein the biological sample is blood.

4. A method according to claim 1 wherein said detection step involves collecting a sample of biological material containing ApoE from the subject.

5. A method according to claim 4, wherein the biological sample is cerebrospinal fluid.

L6 ANSWER 13 OF 16 USPATFULL
1999:99540 Genetic markers used jointly for the diagnosis of Alzheimer's disease, and diagnostic method and kit.
Amouyel, Philippe, Marcq En Baroeul, France
Chartier-Harlin, Marie-Christine, Villeneuve D'Aso, France
Institut Pasteur de Lille, Lille Cedex, France (non-U.S. corporation) Institut National de la Sante et de la Recherche Medicale, Paris Cedex, France (non-U.S. government)
US 5942392 19990824
WO 9524504 19950915
APPLICATION: US 1997-702548 19970102 (8)
WO 1995-FR259 19950306 19970102 PCT 371 date 19970102 PCT 102(e) date
PRIORITY: FR 1994-2603 19940307
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Combined use of at least two genetic markers selected from apolipoprotein E, D19S178 and apolipoprotein CII, for the diagnosis of Alzheimer's disease, especially apolipoprotein .epsilon.4, long apolipoprotein CII (30.+-.3 repeat patterns (CA) and short D19S178 (less than 167.+-.4 nucleotides) alleles. The invention also concerns a method for the diagnosis of Alzheimer's disease and a kit for carrying out said method.

CLM What is claimed is:
1. A method of predicting an increased risk of a patient having Alzheimer's disease or developing Alzheimer's disease , comprising: amplifying the DNA in a DNA-containing biological sample from a patient with a first pair of primers and a second pair of primers which amplify (1) at least a portion of the APOE gene and at least a portion of the APO CII gene, respectively, or (2) at least a portion of the APOE gene and at least a portion of the D19S178 gene, respectively; and assaying for the presence of (1) the APOE .epsilon.4 allele and the long APO CII allele or (2) the APOE .epsilon.4 allele and the short D19S178 allele, wherein the presence of (1) the APOE .epsilon.4 allele and the long APO CII allele or (2) the APOE .epsilon.4 allele and the short

D19S178 allele indicates an increased risk for the patient having Alzheimer's disease or developing Alzheimer's disease
.

2. The method of claim 1, wherein the first pair of primers and the second pair of primers amplify at least a portion of the APOE gene and at least a portion of the APO CII gene, respectively, and said method comprises assaying for the presence of the APOE .epsilon.4 allele and the long APO CII allele in the assaying step.

3. The method of claim 1, wherein the first pair of primers and the second pair of primers amplify at least a portion of the APOE gene and at least a portion of the D19S178 gene, respectively, and said method comprises assaying for the presence of the APOE .epsilon.4 allele and the short D19S178 allele in the assaying step.

4. The method of claim 1, wherein the short D19S178 allele contains fewer than 167.+-.4 nucleotides.

5. The method of claim 4, wherein the short D19S178 allele contains fewer than 167 nucleotides.

6. The method of claim 1, wherein the long APO CII allele contains more than 30.+-.3 cytosine-adenine repeat motifs.

7. The method of claim 6, wherein the long APO CII allele contains more than 30 cytosine-adenine repeat motifs.

8. The method of claim 1, wherein the DNA in the sample is rendered accessible to hybridization with the primers prior to the amplifying step.

9. The method of claim 1, wherein the DNA in the sample is amplified by the polymerase chain reaction (PCR).

10. The method of claim 1, wherein the presence of said alleles is assayed by polyacrylamide gel electrophoresis.

11. The method of claim 1, wherein at least region 112-158 of the APOE gene is amplified in the amplifying step.

12. The method of claim 1, wherein at least the 5' end of the APO CII gene is amplified in the amplifying step.

13. A method of predicting an increased risk of a patient having Alzheimer's disease or developing Alzheimer's disease
, comprising: amplifying the DNA in a DNA-containing biological sample from a patient with a first pair of primers which amplify at least a portion of the APOE gene, a second pair of primers which amplify at least a portion of the APO CII gene, and a third pair of primers which amplify at least a portion of the D19S178 gene; and assaying for the presence of the APOE .epsilon.4 allele, the long APO CII allele, and the short D19S178 allele, wherein the presence of the APOE .epsilon.4 allele, the long APO CII allele, and the short D19S178 allele indicates an increased risk for the patient having Alzheimer's disease or developing Alzheimer's disease.

14. The method of claim 13, wherein the short D19S178 allele contains fewer than 167.+-.4 nucleotides.

15. The method of claim 13, wherein the short D19S178 allele contains fewer than 167 nucleotides.

16. The method of claim 13, wherein the long APO CII allele contains more than 30.+-.3 cytosine-adenine repeat motifs.

17. The method of claim 13, wherein the DNA in the sample is rendered accessible to hybridization with the primers prior to the amplifying step.

18. The method of claim 13, wherein the DNA in the sample is amplified by the polymerase chain reaction (PCR).

19. The method of claim 13, wherein the presence of said alleles is assayed by polyacrylamide gel electrophoresis.

20. The method of claim 13, wherein at least region 112-158 of the APOE gene is amplified in the amplifying step.

21. The method of claim 13, wherein at least the 5' end of the APO CII gene is amplified in the amplifying step.

22. A kit, comprising: a first pair of primers and a second pair primers which are capable of amplifying (1) at least a portion of the APOE gene and at least a portion of the APO CII gene, respectively, or (2) at least a portion of the APOE gene and at least a portion of the D19S178 gene, respectively; a first reagent and a second reagent for assaying for the presence in a DNA sample of (1) the APOE .epsilon.4 allele and the long APO CII allele, respectively, or (2) the APOE .epsilon.4 allele and the short D19S178 allele, respectively, wherein the first reagent and the second reagent are each a probe specific for the respective allele.

23. The kit of claim 22, wherein the first pair of primers and the second pair primers are capable of amplifying at least a portion of the APOE gene and at least a portion of the APO CII gene, respectively, and the kit further comprises a third pair of primers which is capable of amplifying at least a portion of the D19S178 gene.

24. The kit of claim 22, wherein the first pair of primers and the second pair primers are capable of amplifying at least a portion of the APOE gene and at least a portion of the D19S178 gene, respectively, and the kit further comprises a third pair of primers which is capable of amplifying at least a portion of the APO CII gene.

25. The kit of claim 22, further comprising at least one reagent for amplifying DNA.

26. The kit of claim 22, further comprising at least one reagent for performing polyacrylamide gel electrophoresis.

L6 ANSWER 8 OF 16 USPATFULL
2001:97612 Method for determining the prognosis of a patient with a neurological disease.
Sevigny, Pierre, Montreal, Canada
Wiebusch, Heiko, Montreal, Canada
Schappert, Keith, Montreal, Canada
Nova Molecular, Inc., Montreal, Canada (non-U.S. corporation)
US 6251587 B1 20010626
APPLICATION: US 1997-991850 19971216 (8)
DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method for the determining the prognosis for a patient diagnosed with a neurological disease. The present invention also provides a method for the identification of human subjects for placement in clinical drug trials of drugs being tested for the treatment of neurological disease and for determining a patient's future disease risk.

CLM What is claimed is:

1. A method of determining the prognosis for a patient already diagnosed with one of the following neurological diseases: Parkinson's disease, multiple sclerosis, or stroke, said method comprising: a) identifying a patient with said disease; b) determining the apoE genotype or phenotype of said patient; c) converting the data obtained in step b) into a prognosis for said patient.

2. The method of claim 1, wherein said prognosis includes a prediction of drug efficacy, patient outcome, or a forecast of patient disease risk.

3. The method of claim 1, wherein the method further comprises determining the BChE genotype or phenotype of said patient.

4. The method of claim 1, wherein said method further comprises obtaining a patient profile.

5. The method of claim 4, wherein said patient profile includes a determination of said patient's sex.

6. The method of claim 4, wherein said patient profile includes the genotype of said patient.

7. The method of claim 4, wherein said patient profile includes the age of said patient.

8. A method for identifying a patient in a clinical trail of a drug for the treatment of one of the following neurological diseases: Parkinson's disease, multiple sclerosis, or stroke, said method comprising: a) identifying a patient already diagnosed with said disease or as being predisposed to acquire or be at risk for said disease; b) determining the apoE genotype or phenotype of said patient; c) converting the data obtained in step b) and determining the prognosis of said patient, said prognosis including a prediction of whether the patient is a candidate for a drug trial for the treatment of said disease.

9. The method of claim 8, wherein said method further comprises determining the BChE genotype or phenotype of said patient.

10. The method of claim 8 wherein said drug is from the group comprising antithrombotics, cholinomimetics, dopaminergics, and interferon .beta.-1B.

11. The method of claim 8 wherein said drug is tacrine.

12. The method of claim 8 wherein said patient is asymptomatic.

13. A method of determining a prognosis of future risk of a neurological disease, selected from the group

consisting of Parkinson's disease, multiple sclerosis, and stroke, for a mammal asymptomatic for said disease, said method comprising: a) determining the apoE genotype or phenotype of said mammal; b) converting the data obtained in step a) into a prognosis for said mammal, said prognosis including a prediction of said mammal's future disease risk, drug treatment efficacy for said disease, or treatment outcome.

14. The method of claim 13, wherein said mammal is a human.

15. The method of claim 13, wherein the method further comprises determining the BChE genotype or phenotype of said mammal.

16. The method of claim 13, wherein said method further comprises obtaining a patient profile of said mammal.

17. The method of claim 16 wherein said patient profile includes a determination of said mammal's sex.

18. The method of claim 16, wherein said patient profile includes the genotype of said mammal.

19. The method of claim 16, wherein said patient profile includes the age of said mammal.

20. The method of claim 1, wherein the presence of at least one apoE4 allele worsens said prognosis.

21. The method of claim 1, wherein said patient is diagnosed as having stroke or as being predisposed to sustain a stroke.

22. The method of claim 1, wherein said patient is diagnosed as having Parkinson's disease or as being predisposed to acquire Parkinson's disease.

23. The method of claim 1, wherein said patient is diagnosed as having multiple sclerosis or as being predisposed to acquire multiple sclerosis.

24. The method of claim 8, wherein said drug is levodopa-carbidopa.

25. The method of claim 8, wherein said drug is selected from the group consisting of aspirin and ticlopidine.

L6 ANSWER 3 OF 16 USPATFULL
2002:115996 Method for diagnosing Alzheimer disease.
Chartier-Harlin, Marie-Christine, Wattignies, FRANCE
Lambert, Jean-Charles, Lille, FRANCE
Amouyel, Philippe, Marcq en Baroeul, FRANCE
Institut Pasteur de Lille, Lille, FRANCE (non-U.S. corporation)Institut National de la Santa et de la Recherche Medicale (Inserm), Paris, FRANCE (non-U.S. corporation)
US 6391553 B1 20020521
WO 9901574 19990114
APPLICATION: US 2000-446893 20000316 (9)
WO 1998-FR1394 19980630 20000316 PCT 371 date
PRIORITY: FR 1997-8284 19970701
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns a method for diagnosing Alzheimer disease

, consisting in demonstrating one or several mutations in the genomic DNA region regulating the expression of the apolipoprotein E gene, inducing a modification of the apolipoprotein E gene, with respect to a control population or a modification of the expression relative to the alleles of the apolipoprotein E gene.

CLM What is claimed is:
1. A method of detecting the susceptibility of a patient to Alzheimer's disease, which comprises (a.sub.1) determining the level of expression of the .epsilon.4 allele of the gene encoding apolipoprotein E in patients heterozygous, .epsilon.4/.epsilon.3 or .epsilon.4/.epsilon.2, for the apolipoprotein E genotype .epsilon., wherein susceptibility to Alzheimer's disease is indicated by the presence of a mutation in the consensus sequence binding the Th1/E47cs transcription factor and an increase in the level of expression of the .epsilon.4 allele compared to a control population; or (a.sub.2) determining the level of expression of the .epsilon.2 allele of the gene encoding apolipoprotein E in patients carrying the apolipoprotein E genotype .epsilon.2/.epsilon.3, wherein susceptibility to Alzheimer's disease is indicated by the presence of a mutation in the consensus sequence binding the Th1/E47cs transcription factor and a decrease in the level of expression of the .epsilon.2 allele compared to a control population.

2. The method according to claim 1, further comprising (b) identifying a G to T substitution within the consensus binding sequence TH1/E47cs at 186 bases from the first nucleotide of the TATA box of the gene encoding human apoE, wherein the presence of the mutation indicates a susceptibility to Alzheimer's disease.

3. The method according to claim 1, wherein a biological sample selected from the group consisting of cerebral tissue, lymphocytes, fibroblasts and other tissues capable of exhibiting a difference in expression of .epsilon. alleles of the apolipoprotein E gene is used to identify the mutation and to determine the levels of expression of the .epsilon.4 or .epsilon.2 allele with respect to the other allele.

4. A method of detecting the susceptibility of a patient to Alzheimer's disease independent of an .epsilon. polymorphism, which comprises identifying a mutation in the promoter region of the gene encoding apolipoprotein E in the consensus sequence binding the Th1/E47cs transcription factors; wherein the presence of the heterozygous mutation indicates a susceptibility to Alzheimer's disease.

5. The method according to claim 4, wherein the mutation exists in a region situated at 186 bases from the the first nucleotide TATA box of the gene encoding human apoe.

6. The method according to claim 4, wherein a biological sample selected from the group consisting of cerebral tissue, lymphocytes, fibroblasts and other tissues capable of exhibiting a difference in expression of .epsilon. alleles of the apolipoprotein E gene is used to identify the mutation.

L6 ANSWER 1 OF 16 USPATFULL
2002:164672 Method for determining the prognosis of a patient with a neurological disease.
Sevigny, Pierre, Montreal, CANADA
Wiebusch, Heiko, Montreal, CANADA
Schappert, Keith, Montreal, CANADA

US 2002086290 A1 20020704
APPLICATION: US 2000-548540 A1 20000413 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method for the determining the prognosis for a patient diagnosed with a neurological disease. The present invention also provides a method for the identification of human subjects for placement in clinical drug trials of drugs being tested for the treatment of neurological disease and for determining a patient's future disease risk.

CLM What is claimed is:

1. A method of determining the prognosis for a patient already diagnosed with a non-AD neurological disease, said method comprising: a) identifying a patient with said disease; b) determining the apoE genotype or phenotype of said patient; c) converting the data obtained in step b) into a prognosis for said patient.

2. The method of claim 1, wherein said prognosis includes a prediction of drug efficacy, patient outcome, or a forecast of patient disease risk.

3. The method of claim 1, wherein the method further comprises determining the BChE genotype or phenotype of said patient.

4. The method of claim 1, wherein said method further comprises obtaining a patient profile.

5. The method of claim 4, wherein said patient profile includes a determination of said patient's sex.

6. The method of claim 4, wherein said patient profile includes the genotype of said patient.

7. The method of claim 4, wherein said patient profile includes the age of said patient.

8. The method of claim 1, wherein said patient is diagnosed with a disease or determined as being predisposed to a disease selected from the group consisting of stroke, Parkinson's disease, multiple sclerosis, multi-infarct dementia (MID), vascular dementia, cardiovascular injury, and cardiovascular accident.

9. The method of claim 1, wherein said patient is diagnosed as having stroke or as being predisposed to sustain a stroke.

10. The method of claim 1, wherein said patient is diagnosed as having Parkinson's disease or as being predisposed to acquire Parkinson's disease.

11. The method of claim 1, wherein said patient is diagnosed as having multiple sclerosis or as being predisposed to acquire multiple sclerosis.

12. A method for identifying a patient for participation in a clinical trail of a drug for the treatment of a neurological disease, said method compromising: a) identifying a patient already diagnosed with said disease or as being predisposed to

acquire or be at risk for said disease; b) determining the apoE genotype or phenotype of said patient; c) converting the data obtained in step b) and determining the prognosis of said patient, said prognosis including a prediction of whether the patient is a candidate for a drug trial for the treatment of a neurological disease.

13. The method of claim 12, wherein said method further comprises determining the BChE genotype or phenotype of said patient.

14. The method of claim 12 wherein said drug is from the group comprising aspirin, antithrombotics, ticlopidine, Ticlid.TM., cholinomimetics, tacrine, levodopa-carbidopa, Sinernet.TM., interferon .beta.-1B, or Betaseron.TM..

15. The method of claim 12 wherein said drug is tacrine.

16. The method of claim 12 wherein said patient is asymptomatic.

17. A method of determining a prognosis of future risk of a disease for a mammal asymptomatic for said disease, said method comprising: a) determining the apoE genotype or phenotype of said mammal; b) converting the data obtained in step a) into a prognosis for said human, said prognosis including a prediction of a human's future disease risk, drug treatment efficacy for said disease, or treatment outcome.

18. The method of claim 17, wherein said mammal is a human.

19. The method of claim 17, wherein the method further comprises determining the BChE genotype or phenotype of said mammal.

20. The method of claim 17, wherein said method further comprises obtaining a patient profile of said mammal.

21. The method of claim 20, wherein said patient profile includes a determination of said mammal's sex.

22. The method of claim 20, wherein said patient profile includes the genotype of said mammal.

23. The method of claim 20, wherein said patient profile includes the age of said mammal.

24. A kit for determining a prognosis, said kit including a means for converting the patient profile into a prognosis.

25. The kit of claim 24, wherein said kit contains a means for performing the steps of said conversion.

26. The kit of claim 24, wherein said kit contains a means for compiling the data for said patient profile.

27. The kit of claim 24, wherein said kit contains a computer software program to perform the data analysis.

L8 ANSWER 6 OF 7 WPIDS
AN 1996-117154 [12] WPIDS
CR 1996-105768 [11]
DNN N1996-097893 DNC C1996-037211
TI Prognosis of chronic neuro-degenerative pathology following head injury - by detection of ApoE isoforms in the subject's blood or cerebrospinal fluid..
DC B04 S03
IN GRAHAM, D I; NICOLL, J A R; ROBERTS, G W
PA (SMIK) SMITHKLINE BEECHAM PLC; (UNIU) UNIV GLASGOW
CYC 64
PI **WO 9603656 A1 19960208** (199612)* EN 16p
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG US UZ VN
AU 9531144 A 19960222 (199621)
US 5747260 A 19980505 (199825)
ADT WO 9603656 A1 WO 1995-EP2827 19950713; AU 9531144 A AU 1995-31144 19950713; US 5747260 A WO 1995-EP2827 19950713, US 1997-776356 19970225
FDT AU 9531144 A Based on WO 9603656; US 5747260 A Based on WO 9603656
PRAI GB 1994-15073 19940727

AB WO 9603656 A UPAB: 20000617
Prognosis in a head-injured subject (or a subject at risk of sustaining a head-injury) for the likelihood that such an injury might give rise to a chronic neurodegenerative pathology which could result in neuro-psychological, psychiatric or neurological defects, comprises detecting the presence or absence of ApoE isoforms or DNA encoding such isoforms in the subject.

Detection of the ApoE isoforms is carried out ex vivo and involves collection of a sample e.g. blood of cerebrospinal fluid, from the patient.

USE - The method improves clinical prognosis of patients who have suffered a degree of brain damage following a head injury. It may also be used to define the degree of risk to individuals who may be at risk of sustaining a head injury through professional or social activities such as boxing, diving, other sports, or through elective medical procedures such as brain surgery.

ADVANTAGE - The improved prognosis provided by the new method can be used to maximise clinical care for patients and in the design and analysis of clinical trials to determine the efficacy of therapeutic agents.
Dwg.0/0

L16 ANSWER 4 OF 5 MEDLINE
97146628 Document Number: 97146628. PubMed ID: 8993484.
Apolipoprotein E and Alzheimer's disease. A rapidly expanding field with medical and epidemiological consequences. Roses A D. (Department of Medicine (Neurology), Joseph and Kathleen Bryan Alzheimer's Disease, Research Center, Duke University Medical Center, Durham, North Carolina 27710, USA.) ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1996 Dec 16) 802 50-7. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB The Alzheimer's Association and the National Institute on Aging sponsored a meeting of experts in Alzheimer's disease (AD), geneticists, social scientists, and ethicists in Chicago in October 1995 to discuss the use of apolipoprotein E (APOE) genotyping in Alzheimer's disease. A short scientific report was published in the scientific journal Lancet with recommendations from the group. Several areas were discussed, including: (1) the scientific basis for recommendations on the application and uses of APOE genotyping, (2) clarifying the clinical and epidemiological research that needs to done, (3) genetic counseling issues, (4) ethical and legal issues, and (5) potential uses of APOE genotyping for treatment care planning. This contribution was a general introduction to begin the meeting. The genetic association of APOE genotypes with the age of onset distribution and risk of Alzheimer's disease was reviewed. An analysis of the current applications for three distinctly different applications of APOE genotyping was presented with the following conclusions: (1) predictive testing for cognitively intact persons was not recommended; (2) APOE genotyping is a promising adjunct for use in the differential diagnosis of patients with dementia; and (3) APOE genotyping may have a use in selecting therapies; however, further prospective studies are necessary. There is no universal "APOE test for AD." A strong emphasis was made to avoid use of the term in making recommendations regarding APOE genotyping without specific reference to the type of application involved. The predictive testing of asymptomatic persons versus APOE genotyping as a diagnostic adjunct for symptomatic patients has been seriously confused in both the lay and clinical press. The former application is not recommended, but diagnostic usefulness early in clinical evaluations for dementia has been confirmed.

L22 ANSWER 1 OF 1 MEDLINE
95057605 Document Number: 95057605. PubMed ID: 7968026. The apolipoprotein E alleles as major susceptibility factors for Creutzfeldt-Jakob disease. The French Research Group on Epidemiology of Human Spongiform Encephalopathies. Amouyel P; Vidal O; Launay J M; Laplanche J L. (Service d'Epidemiologie, Institut Pasteur de Lille, France.) **LANCET, (1994 Nov 12) 344 (8933) 1315-8.** Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Creutzfeldt-Jakob disease (CJD) is a rapid progressive mental and neurological disorder characterised by dementia and is both infectious and genetic. Pathogenic mutations and a predisposing polymorphism have been described in the prion protein gene and an abnormal prion product accumulates in the brain of affected patients. Apolipoprotein E (APOE), a protein of lipid metabolism, has been detected in some prion protein deposits. This ApoE exists as three common isoforms, coded by specific allele (epsilon 2, epsilon 3, epsilon 4). The presence of at least one epsilon 4 allele was described as a major risk factor for Alzheimer's disease, another neurodegenerative disorder. From a

series of 61 patients with CJD we found that epsilon 4 allele of the APOE gene was a risk factor for the disease ($p < 0.01$). This association was observed in both definite and probable cases, and for patients with and without prion protein gene mutations. Moreover, in affected subjects, epsilon 2 allele of the APOE gene delayed occurrence of death ($p < 0.01$) independently of other known mutations influencing the phenotype of the disease. These effects on neurodegenerative disease associated with APOE alleles suggest a strong involvement of the APOE locus in brain metabolism.

L30 ANSWER 2 OF 5 MEDLINE
1999422399 Document Number: 99422399. PubMed ID: 10492731. Risk of dementia in parents of probands with and without the apolipoprotein E4 allele. The EVA study. Danet S; Brousseau T; Richard F; Amouyel P; Berr C. (INSERM U360, Paris, France.) JOURNAL OF EPIDEMIOLOGY AND COMMUNITY HEALTH, (1999 Jul) 53 (7) 393-8. Journal code: 7909766. ISSN: 0143-005X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB STUDY OBJECTIVE: Age, family history of dementia and the epsilon 4 allele of the apolipoprotein E gene have been associated with Alzheimer's disease (AD). Considering the strength of APOE-epsilon 4 as a genetic risk factor for AD, this factor might explain a large part of the association between AD and a family history of dementia. Therefore, in the general population, a higher frequency of dementia should be observed among parents of probands with at least one epsilon 4 allele than in parents of probands without this allele. DESIGN, SETTING, AND PARTICIPANTS: The study investigated a sample of 1153 volunteers between 59 and 71 years old, genotyped for the APOE gene, all participating in the EVA study. Dementia in their parents was determined using a self reported questionnaire. MAIN RESULTS: The frequency of dementia in 2164 parents was examined and it was found that 245 were demented. The percentage of demented parents was 13.0% in the subgroup of parents of subjects having one or two epsilon 4 alleles and 10.8% in the other subgroup. The relative risk of dementia among parents according to the APOE-epsilon 4 status of probands, was calculated using a Cox model adjusted for the educational level of parents and their history of stroke: RR = 1.21 (95% CI 0.90, 1.63). CONCLUSION: This lack of association supports the observation that in the general population, APOE-epsilon 4 cannot explain a large part of family history of dementia.

L31 ANSWER 2 OF 8 MEDLINE
1998366015 Document Number: 98366015. PubMed ID: 9700658. Apolipoprotein E4, cholinergic integrity and the pharmacogenetics of Alzheimer's disease. Poirier J; Sevigny P. (McGill Centre for Studies in Aging, Douglas Hospital Research Centre, Quebec, Canada.) JOURNAL OF NEURAL TRANSMISSION. SUPPLEMENTUM, (1998) 53 199-207. Ref: 38. Journal code: 0425126. ISSN: 0303-6995. Pub. country: Austria. Language: English.

AB Recent evidence indicates that apolipoprotein E (apoE) plays a central role in the brain's response to injury. The coordinated expression of apoE and its receptors (the so-called LDL receptor family) appears to regulate the transport and internalization of cholesterol and phospholipids during the early phase of the reinnervation process in the adult brain. During dendritic remodelling and synaptogenesis, neurons progressively repress the synthesis of cholesterol in favor of cholesterol internalization through the apoE/LDL receptor pathway. The discovery a few years ago that the apolipoprotein E4 allele found normal in 15% of the normal population is strongly linked to both sporadic and familial late onset Alzheimer's disease (AD) raises the possibility that a dysfunction of the lipid transport system associated with compensatory sprouting and synaptic

remodelling could be central to the AD process. The role of apoE in the CNS is particularly important in relation to cholinergic system which relies to a certain extent on the integrity of phospholipid homeostasis in neurons. Recent evidence obtained in our laboratory indicates that apo epsilon 4 allele has a direct impact on cholinergic system activity in the brain as well as on drug efficacy profile in AD subjects treated with cholinomimetic agents.

L37 ANSWER 106 OF 114 MEDLINE
94309821 Document Number: 94309821. PubMed ID: 8035940. The apolipoprotein epsilon 4 allele in Parkinson's disease with and without dementia. Marder K; Maestre G; Cote L; Mejia H; Alfaro B; Halim A; Tang M; Tycko B; Mayeux R. (G.H. Sergievsky Center, Columbia University, New York, NY 10032.) **NEUROLOGY, (1994 Jul) 44 (7) 1330-1.** Journal code: 0401060. ISSN: 0028-3878. Pub. country: United States. Language: English.

AB The epsilon 4 isoform of apolipoprotein E (Apo-E) may confer genetic susceptibility for familial and sporadic Alzheimer's disease (AD). Because dementia in AD and Parkinson's disease (PD) share many biologic and clinical features, we determined the Apo-E genotypes for 79 patients with PD, 22 of whom were demented, and for 44 age-matched healthy elderly controls from the same community. We hypothesized that if the dementia was similar to AD, there would be a higher allele frequency of apolipoprotein epsilon 4 (Apo epsilon 4) in demented PD patients compared with nondemented PD patients and controls. The epsilon 4 allele frequency for PD without dementia was 0.132, for PD with dementia, 0.068, and for controls, 0.102. There was no association between Apo epsilon 4 and dementia in the PD patients. **We conclude that the biologic basis for dementia in PD may differ from that of AD.**

L37 ANSWER 97 OF 114 MEDLINE
95214666 Document Number: 95214666. PubMed ID: 7700274. Apo E genotypes in multiple sclerosis, Parkinson's disease, schwannomas and late-onset Alzheimer's disease. Rubinsztein D C; Hanlon C S; Irving R M; Goodburn S; Evans D G; Kellar-Wood H; Xuereb J H; Bandmann O; Harding A E. (East Anglian Regional Genetics Service Molecular Genetics Laboratory, Addenbrooke's NHS Trust, Cambridge, UK.) **MOLECULAR AND CELLULAR PROBES, (1994 Dec) 8 (6) 519-25.** Journal code: 8709751. ISSN: 0890-8508. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Apolipoprotein E (apo E) exists in three allelic, functionally distinct isoforms (apo E2, E3 and E4). Recent work has suggested that apo-E-dependent uptake of lipoproteins may play important roles in the development and maintenance of the nervous system and in the responses to both peripheral and central nervous system injury. If apo-E-mediated transport of lipids were a rate-limiting step in these processes, one might expect that the functional differences between the alleles would be associated with varying predispositions to neurodegenerative and demyelinating diseases. Thus, we looked for an association between particular apo E genotypes and susceptibility to multiple sclerosis and Parkinson 's disease. If apo-E-mediated cholesterol uptake were limiting in neuronal growth, one might also expect that apo E2 alleles would slow CNS tumour growth. Accordingly, **apo E genotypes were investigated in individuals with sporadic vestibular schwannomas and neurofibromatosis type 2 (NF-2). No significant alteration in the apo E allele distributions was observed in any of these conditions, nor did the apo E genotypes correlate with disease**

severity. However, we confirmed the previous findings of an over-representation of the apo E4 allele in autopsy-diagnosed late-onset Alzheimer's disease patients. In addition, our data supported the recent observations that apo E2 may be associated with a protective effect for late-onset Alzheimer's disease. These contrasting risks associated with the apo E2 and E4 alleles strengthen the suggestions that this gene is directly involved in the pathogenesis of Alzheimer's disease.

L37 ANSWER 80 OF 114 MEDLINE
96439653 Document Number: 96439653. PubMed ID: 8841967. Molecular biology of APO E alleles in Alzheimer's and non-Alzheimer's dementias. Morris C M; Massey H M; Benjamin R; Leake A; Broadbent C; Griffiths M; Lamb H; Brown A; Ince P G; Tyrer S; Thompson P; McKeith I G; Edwardson J A; Perry R H; Perry E K. (MRC Neurochemical Pathology Unit, Newcastle General Hospital, Newcastle upon Tyne, Tyne and Wear, United Kingdom.) **JOURNAL OF NEURAL TRANSMISSION. SUPPLEMENTUM, (1996) 47 205-18.** Journal code: 0425126. ISSN: 0303-6995. Pub. country: Austria. Language: English.

AB Current research into the aetiology of the dementias is focused upon genetic factors which give rise to the disease process. Recently the Apolipoprotein E gene (APO E) and in particular the epsilon 4 allele has been shown to be a risk factor for late onset Alzheimer's disease (AD) where there is an increased frequency of the epsilon 4 allele. The epsilon 4 allele has also been shown to reduce the age at onset of dementia in AD in a dose dependent manner, with the epsilon 2 allele having an opposing effect. We have genotyped a large series of clinically and neuropathologically confirmed cases of AD and found the expected increase in the Apolipoprotein epsilon 4 allele frequency when compared to a control population. Similarly, in Lewy Body Dementia (LBD) an increased epsilon 4 frequency is also found though a normal epsilon 2 frequency exists, unlike in AD where the epsilon 2 frequency is reduced. **No changes in APO E allele frequencies were found in presenile AD, Parkinson's disease with or without dementia, or in Down's syndrome. No association was found between any of the APO E alleles and the histopathological indices of AD, cortical senile plaques and neurofibrillary tangles, in any disease category. Neurochemical indicators of AD, loss of choline acetyltransferase activity was also unaffected by APO E genotype. Whilst their appears to be a strong association between the APO E allele and AD and also in LBD, other related neurodegenerative disorders associated with dementia do not show such a linkage.** Changes in the epsilon 2 allele frequency may indicate a genetic difference between AD and LBD. The epsilon 4 allele does not appear to influence the burden of AD type pathology and this is particularly relevant given the relative lack of NFT in LBD indicating that factors other than SP or NFT may govern the onset of dementia.

L37 ANSWER 78 OF 114 MEDLINE
97020643 Document Number: 97020643. PubMed ID: 8867021. Apolipoprotein E polymorphism in patients with different neurodegenerative disorders. Helisalmi S; Linnaranta K; Lehtovirta M; Mannermaa A; Heinonen O; Ryynanen M; Riekkinen P Sr; Soininen H. (Department of Neurology, Kuopio University Hospital and University of Kuopio, Finland.) NEUROSCIENCE LETTERS, (1996 Feb 16) 205 (1) 61-4. Journal code: 7600130. ISSN: 0304-3940. Pub. country: Ireland. Language: English.

AB Apolipoprotein E (ApoE) is associated with Alzheimer's disease (AD) neurofibrillary tangles and beta-amyloid protein in senile plaques.

There are three common alleles of ApoE, designated epsilon 2, epsilon 3 and epsilon 4. We studied Finnish patients with neurodegenerative disorders: AD, vascular dementia (VAD), Parkinson's disease (PD), PD+dementia (PDD), Lewy body variant of AD (LB), frontal dementia (FD), and Down's syndrome (DS), as well as control individuals (C). The ApoE genotypes and corresponding allele frequencies of 188 patients and 60 controls were determined by digestion of ApoE polymerase chain reaction products with the restriction enzyme Hha I. The ApoE epsilon 4 allele frequency was 0.17 for C, 0.44 for AD, 0.35 for VAD, 0.10 for PD, 0.38 for PDD, 0.28 for LB, 0.39 for FD, and 0.17 for DS. We found significant differences in genotype frequency between AD/C, AD/PD and AD/DS. Our results suggest that, beside AD, an increased frequency of epsilon 4 may also be involved in other dementing neurological disorders.

L37 ANSWER 45 OF 114 MEDLINE
1999011031 Document Number: 99011031. PubMed ID: 9797007.
Apolipoprotein E epsilon4 allele frequency is increased in Parkinson's disease only with co-existing Alzheimer pathology.
Mattila P M; Koskela T; Roytta M; Lehtimaki T; Pirttila T A; Ilveskoski E; Karhunen P; Rinne J O. (Department of Neurology, University of Turku, Finland.) **ACTA NEUROPATHOLOGICA, (1998 Oct) 96 (4) 417-20**. Journal code: 0412041. ISSN: 0001-6322. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB We determined the apolipoprotein E (apoE) genotype in clinically diagnosed and neuropathologically verified cases of Parkinson's disease (PD) (n = 45), with or without Alzheimer (AD)-type changes, and compared the apoE genotype with that in healthy age-matched controls (n = 59). The PD cases were divided into two groups according to the CERAD criteria: "O + A", with no or only uncertain histological findings of AD, and "B + C" with histological findings suggestive or indicative of AD. DNA was isolated from frozen brain samples, and the apoE genotypes were determined using polymerase chain reaction amplification and subsequent restriction analysis by HhaI enzyme. The frequency of the apo epsilon4 allele (29.4%) was significantly increased in the B + C group. The odds ratio for an apo epsilon4 allele in the B + C group was 2.5 as compared to controls (95% confidence interval, 1.2-5.2). In the O + A group, the frequency of apo epsilon4 allele (13.6%) was similar to that in controls (14.4%) and the risk of an apo epsilon4 allele was not increased (odds ratio 0.94). The PD cases with an apo epsilon4 allele had a greater number of cortical (P = 0.02) but not nigral Lewy bodies than those without an apo epsilon4 allele (P = 0.57). **The results show that neuropathologically verified PD as such is not associated with increased apo epsilon4 allele frequency**.